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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/469,492	06/06/1995	HOWARD WEINER	1010/16959-U	6384

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/469,492	WEINER ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,42-44,48,52-57 and 66-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,42-44,48,52-57 and 66-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 12-9-04 has been entered into the record. Claims 37, 42-44, 48, 52-57 and 66-72 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

The rejection of claims 37 and 42-44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendment to claim 37.

The rejection of claim 37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claim.

Rejections Maintained

Claims 37, 42-44, 48, 52-54, 56, 57 and new claims 66-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons made of record in the Office Action mailed 6-9-04.

Applicants' arguments have been carefully considered but are not persuasive for reasons set forth herein. Applicants allege that the examiner has mischaracterized Harats WO 02/053092 and reference the citation by Harats of Applicants own successful induction of tolerance by oral and nasal administration of bystander antigens. This is not persuasive; US Patent No. 5,935,557 was filed in 1997, seven years after the priority date of this application. Seven years of information and data had accumulated in the art.

Further, the claims of 5,935,557 and the instant claims are not the same and as such, the issued patent has no bearing on what one of skill in the art would have found enabled or unpredictable "at the time the invention was made" in 1990. The courts have clearly established that enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claimed. *In re Hogan and Banks*, 194 USPQ 527 (1977). Applicants argue that Harats teaches that antigens "should be" adaptable to nasal and other membranous routes of administration and therefore clearly one would readily appreciate that oral administration of the bystander antigens could be extrapolated to nasal administration of a bystander antigen. This is not persuasive "should be" is not a definitive correlation and Applicants ignores all the cited art that teaches unpredictability and Harats et al that teaches that the parameters for induction of oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results and must result from extensive empirical experimentation. Applicants ignore the plethora of teachings of Zivney et al, Hannihen et al, Fujihasi et al and Cousin et al that clearly teach inconsistencies in mucosal tolerance, that the response to one tolerance inducing antigen could not necessarily predict the response to another, and although animal studies have shown promising finding, in humans the work remains highly experimental and a handful of trials have screeched to a halt. Further, the art teaches that human studies of myelin basis protein and collagen as toleragens/suppressive agents provided no clinical benefit and faired no better than control (Marketletter 12, September 1999; of record). Clearly, "should be" as recited in Harats is not what is actually being observed in the art. Applicants argue that the present specification incorporates by reference USSN 07/454,806 that teaches the induction of tolerance by inhalation of myelin basic protein. This is not persuasive; the claim language specifically excludes myelin basic protein (MBP). It is noted that the claims specifically require "wherein in said bystander antigen is not an antigen to which T cells of said host which mediate the disease are sensitized and wherein said bystander is not an insulin

antigen and wherein said bystander antigen is present in an organ or tissue afflicted by immune attach during said disease". The teachings of 07/454,806 are drawn to induction of EAE in a rat using MBP wherein the aerosolized antigen is MBP. As such, this embodiment does not provide enablement for the claimed invention. Applicants also argue the collagen induction in this reference. Again, the name of the game is the claims and the claims specifically exclude this antigen as a bystander antigen because it is an antigen to which the host which mediate the disease are sensitized. The same can be said for type I diabetes and glutamic acid decarboxylase. Applicants argue that the mechanism of bystander suppression is the same, regardless of route of antigen administration. This again is not persuasive, the issue is that the specification as filed, does not teach successful nasal or inhaled administration of a bystander antigen for suppression of an ongoing autoimmune response in an animal model and certainly not in humans as claimed. The issue remains that success for one mode of antigen administration does not predict success with another mode and that success with one antigen does not predict success with another. The available data for humans has been provided and is of record. There is no correlation between animal models and human treatment for tolerance or suppression of an ongoing autoimmune response. Applicants ignore the failures of the art for humans and the lack of correlation of animal models with human efficacy in this art area. Applicants argue that both oral and inhaled administration provides for delivery to the peyers patches of the intestine where the bystander antigen induces suppressive T cells. Applicants argue that success with oral therefore predicts success with inhaled. This is not persuasive, Applicants point out that the inhaled antigen must "travel to the peyers patches" in the small intestine. This is not persuasive, there is no evidence that the inhaled antigen travels to the peyers patches and nasal-associated lymphoreticular tissue in the oropharyngeal cavity stand as sentinels to the respiratory tract and represent the major site where mucosal immune responses are initiated in response to inhaled antigens. The lung itself is also associated with lymph system that contains lymph nodes where

draining lymph containing antigen is presents antigen to the immune system to initiate a response. There for the alleged common basis "the bystander antigen" in the peyers patches of the small intestine is not documented by this specification and is in contrast to the established physiological immune system structures in place in the respiratory tract. Applicants reiterate the teachings of the specification with respect to pages 23-25 and inhaled antigens. This teaching has been considered repeatedly, but lacks any evidence as to the effectiveness in the specification as filed for bystander antigens. Applicants argue that EAE is a model for multiple sclerosis and effective treatment thereof. This is not persuasive, Applicants ignore that the art teaches that human studies of myelin basis protein and collagen as toleragens/suppressive agents provided no clinical benefit and faired no better than control (Marketletter 12, September 1999; of record). Further, Applicants ignore the teachings of the references of Zivney et al, Hannihen et al, Fujihasi et al and Cousin et al that clearly teach inconsistencies in mucosal tolerance and unpredictability in this field of invention. It remains that there is no working example of any bystander antigen that effectively suppresses an ongoing immune response by the nasal or inhaled route and the art teaches that this area is highly unpredictable, the results in animals does not translate to humans. Applicants alleged that the animal models are widely established animal models and correlate with human disease. This is again not persuasive, the art clearly teaches that effects in animal models are not predictive of effects in humans and Applicants ignore the teachings of Zivney et al, Hannihen et al, Fujihasi et al and Cousin et al and Marketletter 12, September 1999; of record. Although animal models including the EAE model can provide important lessons that are applicable to human disorders such as multiple sclerosis, not all such animal models are the same in providing features in common with human diseases, encompassed by the claimed methods. See Swanborg et al. (Clinical Immunology and Pathology 77: 4-13, 1995) and Dijkstra et al. (TIPS Reviews 14: 124-129, 1993). Dijkstra et al teach that in 1993, virtually nothing is known about the induction response of the concerned immune response, nor about the

antigen to which a putative immune response is raised and therefore the EAE model is of doubtful use in addressing questions on the initiation of MS. Although animal models including the EAE model can provide important lessons that are applicable to human disorders such as multiple sclerosis, not all such animal models are the same in providing features in common with human diseases, encompassed by the claimed methods. See Swanborg et al. (Clinical Immunology and Pathology 77: 4-13, 1995) and Dijkstra et al. (TIPS Reviews 14: 124-129, 1993). The model employed in the specification is the acute model and not the chronic relapsing model that has many features in common with multiple sclerosis, the clinical course showing similar relapses and remissions. Dijkstra et al teach that the induction phase of EAE has been studied extensively, however the relevance of the studies for human multiple sclerosis remains to be established (page 215, paragraph bridging columns 2-3). It is noted that the claims specifically address the use of bystander antigens for suppression of an ongoing immune response in a human and specifically contemplate suppression of an ongoing autoimmune response wherein the autoimmune response is in multiple sclerosis (see specification, page 19, Table 1). Tisch et al (Proc. Natl. Acad. Sci, 91:437-438, 1994 of record; page 437, column 2, first full paragraph) teach that spontaneous autoimmune disease such as multiple sclerosis, type I diabetes (IDDM) and rheumatoid arthritis, the autoantigen(s) are not known and a number of autoantigens appear to be involved in the disease process. Unlike the animal model where the specific inducing autoantigen is known, the autoantigens in human disease are not known or multiple ones have been identified (as many as six to eight in IDDM). The initiating antigen for multiple sclerosis in humans was not known at the time of the invention was made. This specification does not teach a human population having spontaneous autoimmune disease that does not have multiple autoantigens. The specification does not teach the inducing autoantigen in humans. Swanborg et al (Clinical and Immunopathology, 77(1):4-13, 1995) teach that proliferative responses to myelin antigens have been observed with lymphocytes form control subjects and an increased

frequency of myelin basis protein and proteolipid reactive T cells in the cerebrospinal fluid of multiple sclerosis patients with MS (see page 6, column 2). The specification does not teach what population of humans can be treated using the claimed method, when the autoimmune diseases may be caused by multiple autoantigens ? How can one chose a bystander according to the invention, when the initiating antigen is not disclosed, known to the art and the art teaches that the autoimmune diseases appear to involve multiple autoantigens. With respect to adjuvant arthritis, this specification is devoid of any data for bystander treatment of inhaled or nasally administered bystander antigens. Applicants argue that Van Eden et al teach that the animal model presented by Van Eden et al teach that the results are applicable to the corresponding human disease. This is not persuasive, the art teaches that arthritis can be induced in susceptible rats by immunization by *Mycobacterium tuberculosis* and that a T cell clone cross-reacts with a proteoglycan purified from collagen. The reference does not teach that therapeutic results achieved in the animal model are predictive of therapeutic results in the corresponding human disease at page 5117 and therefore cannot be relied upon for predictive results in human disease. Applicants argue that the examiner has improperly relied upon Marketletter because the lack of commercial success does not speak to enablement at the time of filing and did not measure suppression. This is not persuasive, the relied upon teaching was not a lack of commercial success but that the reported finding, that the human treatment did not work and was presented to buttress the examiners finding that the use of the animal models did not predict success in humans at the time of filing. Merely, because an animal can be used to study one aspect of a disease process, does not provide any evidence that therapeutic outcomes in the animal model predictably reflects the therapeutic outcome in humans. At the time that this invention was filed, there is no evidence that the models used to study autoimmune disease could be used as therapeutic models to predict success in human treatment. Van Eden et al does not teach the correlation of therapeutic success of the animal models of the specification

with therapeutic success of human disease. Applicants argue that they are not required to provide working embodiments of all of the aspects of the claimed invention and that the absence of a working example does not in and of itself compel the conclusion that the specification is not enabled. This is not persuasive, the presence or absence of working examples is a factor to be considered in enablement. In reaching a conclusion of undue experimentation, the following factors have been considered: quantity of experimentation necessary, amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims (*In re Wands* (CAFC) 8 USPQ2d 1400). Clearly, the record establishes that the examiner has not solely relied upon working examples to establish a lack of enablement. It is noted, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one route of administration, what other routes will work and that tolerance/suppression induction is unpredictable and was highly experimental at the time of filing. Applicants again argue Harats and the Von Herrath declaration and argue that the examiners position is in contrast to that presented by Harats. This is not persuasive, the reliance on Harats et al for the teaching of the patent is not pertinent to the claimed invention because the claims are not of the same scope and nor drawn to the same invention. Further, Applicants ignore the cautioning in Harats et al specifically relied upon by the examiner in combination with the teachings of Zivney et al, Hannihen et al, Fujihasi et al and Cousin et al to demonstrate that the findings are highly experimental, unpredictable, not predictable from one antigen to another and do not readily translate to therapeutic efficacy in humans. The Von Herrath

declaration is not probative of the instantly claimed invention. It is only in specific animal models, not claimed, that one can predict "the antigen to which T cells of said host which modulated that disease are sensitized and wherein said bystander antigen is not an insulin antigen". The claims are not limited to those animal models and induction by specific antigens for which one might be able to choose a "bystander". The record establishes that human disease is heterogeneous and the record establishes that humans have autoimmune responses to all the autoantigens in the bystander list at page 19. Humans, unlike specific animal models do not have a single autoantigenic response. The specification does not teach how a "bystander" can target the heterogeneous response in humans when they have sensitized T cells to the indicated autoantigens. There is no teaching of nasal or inhaled proteolipid protein in a rodent with experimental autoimmune encephalomyelitis (EAE) induced by MBP. The art of record establishes that the route of administration/immunization is not predictable from one route to another, that the effect of one antigen to another is not predictable and that therapeutic effects in models are not predictive of success in humans. The Van Herrath declaration does not cure these deficiencies and in fact relies upon data specifically excluded by the now claimed invention. Although, the alleged mechanism might be the same, this does not establish that the bystander antigen is effective as claimed and that the demonstration of effectiveness in commensurate with the claims. The Van Herrath declaration opines that the conclusions could be extended to bystander antigens but provides no probative evidence to support that conclusion. There remains no evidence of record of nasal or inhaled efficacy of any bystander antigen as set forth in the claims, delivered to an animal model or human wherein it is not an antigen to which T cells of said host which mediate the disease are sensitized. The claim specifically excludes the embodiments relied upon by Declarant to establish enablement for the claimed invention.

The rejection of record is therefore maintained.

New Objections/Rejections Based on Amendment

Claim 66 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims now recite that the bystander is administered to the buccal mucosa of said host by inhalation. Buccal is defined as pertaining to or in the direction of the cheek. Applicants argue that the specification at page 23, lines 25-31 provides support for concept of delivery by inhalation. Page 23, lines 25-31 only pertains to delivery to bronchial or pulmonary mucosa by inhalation. As such, the written description of the specification as filed does not support delivery to the "buccal mucosa" by inhalation as set forth in the claims.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645